Epidemiology of Childhood Hyperthyroidism in France: A Nationwide Population-Based Study

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Context: Hyperthyroidism affects all age groups, but epidemiological data for children are scarce.

Objective: To perform a nationwide epidemiological survey of hyperthyroidism in children and adolescents.

Design: A cross-sectional descriptive study.

Setting: Identification of entries corresponding to reimbursements for antithyroid drugs in the French national insurance database.

Participants: All cases of childhood hyperthyroidism (6 months to 17 years of age) in 2015.

Main Outcome Measures: National incidence rate estimated with a nonlinear Poisson model and spatial distribution of cases.

Results: A total of 670 cases of childhood hyperthyroidism were identified. Twenty patients (3%) had associated autoimmune or genetic disease, with type 1 diabetes and Down syndrome the most frequent. The annual incidence for 2015 was 4.58/100,000 person-years (95% CI 3.00 to 6.99/100,000). Incidence increased with age, in both sexes. This increase accelerated after the age of 8 in girls and 10 in boys and was stronger in girls. About 10% of patients were affected before the age of 5 years (sex ratio 1.43). There was an interaction between age and sex, the effect of being female increasing with age: girls were 3.2 times more likely to be affected than boys in the 10 to 14 years age group and 5.7 times more likely to be affected in the 15 to 17 years age group. No conclusions about spatial pattern emerged.

Conclusion: These findings shed light on the incidence of hyperthyroidism and the impact of sex on this incidence during childhood and adolescence. The observed incidence was higher than expected from the results published for earlier studies in Northern European countries. (***J Clin Endocrinol Metab*** **103: 2980–2987, 2018)**

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Abbreviations: ATD, antithyroid drug; DCIR, Données de consummation inter-régimes; EDC, endocrine-disrupting chemical; GD, Graves disease; IR, incidence rate; NIR, numéro d'inscription au repertoire; PMSI, Programme de médicalisation des systèmes d'information; SNIIRAM, Système national d'information inter-régimes de l'Assurance maladie.

Hyperthyroidism in children is predominantly caused by Graves disease (GD), an autoimmune disorder caused by stimulation of the TSH receptor by autoantibodies specific for this receptor. Increases in the incidence of autoimmune diseases, including type 1 diabetes mellitus and celiac disease, in children and adolescents have been reported in recent years, and a similar increase has been suggested for hyperthyroidism (1–3). Like other autoimmune disorders, GD is thought to result from a complex interaction among genetic background, environmental factors (*e.g.*, iodine status), and the immune system. Moreover, patients often present more than one autoimmune disorder (4).

Endocrine-disrupting chemicals (EDCs) have been identified as potential environmental risk factors. A specific epidemiological program making use of existing databases to monitor nationwide trends for health indicators in the context of EDC exposure (5) in France was launched in 2014 (6). Autoimmune disorders frequently affect the thyroid gland, and thyroid disorders are specific outcomes of interest, as many EDCs act as thyroid disruptors. A few studies have identified molecules that induce increases in thyroid hormone levels: chlorinated pesticides (7–10), bisphenol A (11, 12), polybrominated flame retardants (13, 14), and perfluorinated chemicals (8). In addition to interacting directly with the thyroid gland, thyroid disruptors are thought to interact with the autoimmune system (15–19), potentially triggering thyroid autoimmune diseases, such as GD.

GD, a disease displaying female predominance, is rare and severe in children and adolescents. It is thought to account for 5% (20) of diagnosed cases of hyperthyroidism throughout life, but epidemiological data are limited. Previous studies were subject to selection bias, due to the selection criteria applied to the study populations: outpatients only (21), willingness of the pediatrician to report data (22), and limited study area (23). Moreover, population-based data are required in areas with adequate iodine levels.

GD may adversely affect the health and development of the child, and patients therefore require long-term follow-up. The first-line treatment of newly diagnosed children is based on the use of antithyroid drugs (ATDs) prescribed by clinicians. No other indication for these drugs is known in children, and this treatment is, therefore, specific. Alternative treatments, such as radioiodine and thyroidectomy, are proposed as a second line of treatment in cases of failure to control the disease after ATD treatment (4).

We therefore conducted a nationwide study to estimate the incidence of hyperthyroidism and describe its epidemiology in children and adolescents and analyze spatial trends in France in 2015.

Methods

Data source

We performed a population-based study with the French National Health Insurance Information System, Système national d'information inter-régimes de l'Assurance maladie (SNIIRAM) (24). This system comprehensively covers the entire population living in France (>66 million inhabitants) (25, 26). It records, in a specific database known as Données de consummation inter-régimes (DCIR; interscheme consumption data), anonymous and exhaustive data about patient reimbursement for health care expenditure, including reimbursements for drugs prescribed by clinicians. Drugs are identified in the database according to their Anatomical Therapeutic Classification codes. These data are relayed in real time from the various health insurance schemes. Another database, Programme de médicalisation des systèmes d'information (PMSI), included in SNIIRAM, provides medical information for all patients admitted to public and private hospitals in France, including discharge diagnoses recorded as International Statistical Classification of Diseases and Related Health Problems, 10th revision codes. Demographic data [age, sex, place of residence (département code), and affiliated scheme] are available from the DCIR and PMSI databases. All of the data for a given patient present in the SNIIRAM (DCIR and PMSI) can be linked through anonymous social security identification numbers [numéro d'inscription au repertoire (NIRs)].

The DCIR holds data for 3 years plus the current year. Data for the years 2013, 2014, 2015, and the first 6 months of July 2016 were, therefore, available to us at the time of the study.

The National Institute of Statistics and Economic Studies supplied population data.

Access to the SNIIRAM databases was authorized by the Institute of Health Data (Institut des Données de Santé) and the French data protection authority (Commission Nationale de l'Informatique et des Libertés).

Study population

The selected study population consisted of all individuals under the age of 18 years (age defined as the number of full years of life completed) living in France. Incident cases of hyperthyroidism were defined as the first reimbursement for ATDs (propylthiouracil, benzylthiouracil, carbimazole, and thiamazole) in 2015 recorded in the DCIR, with no reimbursement for ATDs in the 2 preceding years (2013 and 2014), to exclude the resumption of ATD treatment after relapses. Such relapses are common in children with hyperthyroidism, being observed in ~70% to 80% of all cases after an initial 2-year course of ATD treatment, with ~75% of patients relapsing within 6 months of the end of treatment and 95% relapsing within 18 months (27, 28).

We excluded three categories of patients: children under the age of 6 months in 2015, mostly considered to correspond to cases of neonatal transient thyrotoxicosis due to maternal GD (29). Given the difficulties distinguishing between incident cases and relapses, we excluded patients who had undergone surgery (total or subtotal thyroidectomy) or radioiodine treatment in 2015 (n = 1) by linking incident cases of hyperthyroidism to hospital stays including a medical act encoded KCFA010, KCFA009, KCFA005, KCFA007, KCNL003, and KCNL004 (French Common Classification of Medical Procedures codes). We ensured that only the population dwelling in France was

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targeted by excluding records for which the area of residence (département) was not reported or for which the area of residence cited was located outside France (n = 1).

We identified the autoimmune diseases or related conditions associated with hyperthyroidism by linking incident cases of hyperthyroidism with cases of type 1 diabetes mellitus (International Statistical Classification of Diseases and Related Health Problems, 10th revision, E100 to E109), Turner syndrome (Q960 to Q964, Q968, and Q969), Down syndrome (Q900 to Q902 and Q909), DiGeorge syndrome (D821), celiac disease (K900), Addison disease (E271), or idiopathic thrombocytopenic purpura (D693) by cross-referencing with hospital data (PMSI).

Statistical analysis

We described the characteristics of the population and distribution of cases by sex and age group. The sex ratio (girls vs boys) was calculated for the total population and by age group. We explored month-to-month variations graphically to detect a possible seasonal influence on the disease that might be related to environmental exposure. We focused initially on the month of diagnosis and then on birth month.

We estimated incidence rates (IRs) and 95% CIs by Poisson regression analysis using population size as the offset. We used generalized linear models to take into account nonlinear relationships between IRs and the explanatory variables, age and sex. We introduced the age variable into the model as a spline function with three degrees of freedom to take the possibility of a nonlinear relationship into account, and we explored the interaction between age and sex. We assessed the validity of the model by analyzing the distribution of the residuals, which were found to be essentially normally distributed. No trend was seen, and the dispersion of residual values around the mean remained constant.

We estimated IRs for the overall population aged from 6 months to 17 years and by age and sex using the number of predicted cases in 2015 and midyear population estimates for children in France for 2015 (14.8 million children).

For comparison of our results with published values, we converted the age-specific IR values provided by the model into IR values for each age group. The rates for age treated as a continuous variable were calculated from Poisson regression model predictions. For the estimation of IRs by age group, we calculated the weighted mean of IRs for each age in the age group. The weighting used was the inverse of the variance of IR by age. The age groups of interest were 6 months to 4 years, 5 to 9 years, 10 to 14 years, and 15 to 17 years. We also estimated overall IRs for children under 15 years of age (12.3 million children).

We analyzed the spatial distribution of cases in France at the département level (a French administrative region, equivalent to a county), with four models of structured and unstructured spatial heterogeneity based on Poisson regression (30).

Statistical analyses were performed with SAS Guide 7.1 (SAS Institute, Cary, NC) and R for Poisson regression. The model for IR estimation was developed with the generalized linear model procedure implemented in the MGCV package (31) and the INLA model for spatial analyses using R software (32).

Results

Study population and patient characteristics

In total, we identified 670 children newly treated for hyperthyroidism in 2015: 157 boys (23.4%) and 513 girls (76.6%). A female preponderance was documented throughout childhood and adolescence, with a female-to-male sex ratio of 3.27. The ages of the affected children ranged from 6 months to 17 years, and mean age was higher in girls than in boys (Table 1).

The principal ATDs used to treat hyperthyroidism in children and adolescent in 2015 were carbimazole (63% cases), followed by thiamazole (31%), propylthiouracil (5%), and benzylthiouracil (1%). During the observation period, most of the patients (n = 626; 93%) used only one drug. However, 44 patients switched once (n = 40; 6%) or twice (n = 4; 1%) between treatments.

Twenty patients (3%) had associated autoimmune conditions: n = 1 in the 6 months to 4 years, n = 4 in the 5 to 9 years, n = 10 in the 10 to 14 years, and n = 5 in the 15 to 17 years age groups. Table 2 describes the types of autoimmune disease observed by age group and sex. The number of incident cases remained stable from month to month, regardless of whether the analysis was based on month of diagnosis or birth month (data not shown).

Incidence estimation

Figure 1 provides a comprehensive representation of the model. A statistically noteworthy increase in incidence with age was observed after the age of 5 years. Indeed, the inclusion of age or the interaction between age and sex in the Poisson regression model significantly decreased the residual deviance. This effect was visible on the plot, as the regression lines for girls and boys had different slopes, particularly for teenagers.

The increase in IR was more marked from the age of 8 years in girls and 10 years in boys, with a female preponderance observed at all ages. The CIs for IRs were larger for the youngest children, with considerable overlap between the sexes, making it difficult to draw any firm conclusions.

Table 3 presents the sex-specific IRs calculated for several age groups, based on Poisson model predictions. The overall IR for 2015 was 4.58/100,000 person-years (95% CI 3.00 to 6.99/100,000). It was 3.4 times higher

Table 1. Characteristics of the Subjects at the Time of First Reimbursement for ATD Treatment of Hyperthyroidism in Children and Adolescents in France for 2015

	Total (N = 670)	Boys (n = 157; 23.43%)	Girls (n = 513; 76.57%)
Mean age, y	12.5 (4.68)	11.2 (5.36)	13.5 (4.34)
Age group			
6 mo to 4 y	68 (10.20)	28 (17.83)	40 (7.80)
5–9 y	75 (11.20)	24 (15.29)	51 (9.94)
10–14 y	215 (32.10)	56 (35.67)	159 (30.99)
15–17 y	312 (46.60)	49 (31.21)	263 (51.27)

Data are mean (SD).

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Table 2. Associated Autoimmune Diseases in Children and Adolescents First Treated for Hyperthyroidism in 2015 in France by Age Group and Sex

	Associated Disease		
	T1DM (N = 13)[a]	Celiac Disease (N = 2)[a]	Down Syndrome (N = 7)[a]
Age group			
6 mo to 4 y	—	—	1
5–9 y	4	1	1
10–14 y	7	—	3
15–17 y	2	1	2
Sex			
Boys	3	0	2
Girls	10	2	5

No cases of Addison disease, idiopathic thrombocytopenic purpura, Turner syndrome, or DiGeorge syndrome were reported.

Abbreviation: T1DM, type 1 diabetes mellitus.

[a]One patient had T1DM, celiac disease, and Down syndrome.

in girls than in boys [IRs: 7.08 (95% CI 4.85 to 10.30) vs 2.07 (95% CI 1.03 to 4.16)]. The overall IR for 2015 was markedly lower in children under the age of 15 years at 2.91/100,000 person-years (95% CI 2.05 to 4.13/100,000) and was 2.4 times higher in girls than in boys for this age group [IRs: 4.11 (2.91 to 5.83) vs 1.71 (1.00 to 2.93)]. In comparisons by age group, IRs were markedly higher in teenage girls than in teenage boys: 3.2 times higher for the 10 to 14 years age group and 5.7 times higher for the 15 to 17 years age group.

Spatial distribution

Crude IRs by département varied from 0/100,000 person-years to 12.5/100,000 person-years. The spatial models used did not fit our data well, and the results obtained were inconclusive. Some neighboring départements had discrepant incident case numbers, making it impossible to estimate IRs with the necessary level of precision for all départements.

Discussion

In this nationwide French study, our main objective was to improve understanding of the epidemiology of hyperthyroidism in children. We estimated the incidence of this disease from an indicator based on drug reimbursements. In 2015, the IR of hyperthyroidism in children was 4.58/100,000 person-years (2.91/100,000 person-years in children under 15), highlighting the rarity of this disease in children and adolescents. We described IR by age considered as a continuous variable using a nonlinear model to ensure that the most complete information was retained. The IR in girls was markedly higher than that in boys, and this difference increased strongly with age, particularly during the teenage years. The results of this study also extend our knowledge of the incidence of this disease in very young children, because ~10% of the patients in this cohort began receiving treatment before the age of 5 years.

Epidemiological data concerning childhood hyperthyroidism are scarce. Studies have been carried out in Northern Europe and China. Nationwide results were reported, except for the Chinese studies, and all of these studies reported incidence by age and sex for children under the age of 15 years. A Danish study based on the Danish National Patient Registry estimated the IR of childhood hyperthyroidism at 1.83/100,000 person-years for 2008 to 2012 (95% CI 1.47 to 2.25/100,000), the

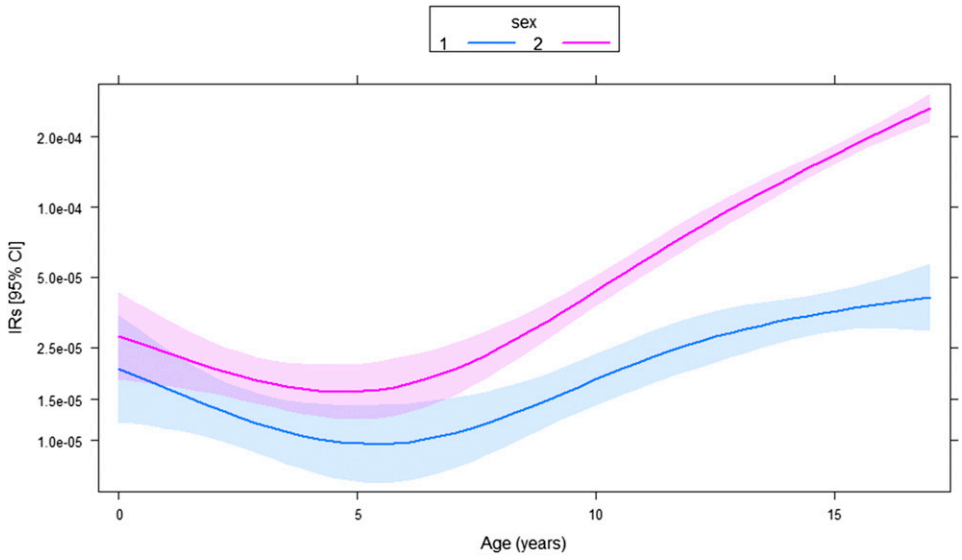

Figure 1. Predicted IRs by age and sex.

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Table 3. Sex-Specific IRs and 95% CIs in Children and Adolescents First Treated for Hyperthyroidism in 2015 by Age Group

	Total		Boys		Girls	
2015	IR[a]	95% CI	IR[a]	95% CI	IR[a]	95% CI
6 mo to 17 y	4.58	3.00–6.99	2.07	1.03–4.16	7.08	4.85–10.30
6 mo to 14 y	2.91	2.05–4.13	1.71	1.00–2.93	4.11	2.91–5.83
6 mo to 4 y	1.53	1.14–2.05	1.30	1.19–1.42	1.80	1.54–2.10
5–9 y	1.85	1.48–2.33	1.26	1.17–1.34	2.25	1.99–2.53
10–14 y	5.28	4.52–6.15	2.48	2.32–2.65	7.89	6.90–9.02
15–17 y	12.03	10.06–14.38	3.78	3.49–4.10	21.53	18.96–24.45

Poisson regression analysis was used to estimate IR and CIs.

[a]Number of cases per 100,000 person-years.

study period closest to that for our study. The incidence reported in the Danish study was lower than that reported in this study by a factor of 1.6, but was calculated 5 years ago, and the CI overlaps with that for our findings. The Swedish studies that most closely resembled ours in those cases were selected based on diagnosis and treatment. It involved a retrospective analysis of medical records and computer-based registers. The authors of the Swedish study estimated the IR at 2.7/100,000 person-years, a value slightly lower than that obtained in this study (2.91/100,000), but with overlapping CIs, suggesting that it is consistent with our results. However, the Swedish study was performed 15 years before our study and included children under the age of 16 years. The two studies are not, therefore, strictly comparable. In a study performed in the Hong Kong area from 1989 to 1998 (33), with a registry of patients with childhood GD, the overall IR was found to be 5.0/100,000 person-years (95% CI 2.6 to 8.8) for children under the age of 15 years. From 1994 to 1998, the IR was 6.5/100,000 person years (95% CI 3.7 to 10.5), a figure much higher than that reported in this study, with no overlap of CIs, and for an earlier period. The authors speculated that their result might reflect high local levels of iodine. The last study, conducted in the United Kingdom and Ireland in 2004 to 2005 (22), considered all new cases of thyrotoxicosis in childhood, collected prospectively from pediatricians only. The overall IR was 0.9 per 100,000 person-years (95% CI 0.8 to 1.1), one-third lower than reported in this study, with no overlap between the CIs of the two studies. However, case reporting was almost certainly not exhaustive, because it depended on the voluntary participation of pediatricians.

Overall, our results are slightly higher, but within the range of previous results, except for those for Hong Kong. However, all of these studies were performed several years or even decades ago, and, to our knowledge, no updated data are available. As previously observed in the studies performed in Denmark, Sweden, and Hong Kong (3, 23, 33), the results suggest that the incidence of childhood hyperthyroidism in France may have increased, but further data are required to confirm this finding.

Other studies have also reported an increase in the frequency of hyperthyroidism with age, peaking during adolescence and affecting girls to a much greater extent than boys. However, the IRs by age group obtained in this study were higher than those reported in other European studies, for all age groups.

In our study, the sex ratio in children under the age of 15 years (girls vs boys, 2.37) was lower than those reported in Denmark (4.3) and China (9.7). A few studies have focused on sex ratio, and, to our knowledge, changes in sex ratio with age have never been investigated for childhood hyperthyroidism. The reason for this sex-related difference is unknown, but autoimmune diseases are generally more frequent in girls, due at least partly to the effects of estrogen (34, 35). Further studies are warranted to explore the crucial role of estrogen, particularly at the time at which serum estrogen levels increase during puberty in girls and, to a lesser extent, in males (34, 36).

Our findings also provide precise information about the prevalence of associated autoimmune conditions in children with hyperthyroidism. They are consistent with those of previous studies in children reporting an association of GD with type 1 diabetes, celiac disease, and Down syndrome (2, 28, 37–39). However, the epidemiological studies reporting these associations were based on a very limited study population of children with hyperthyroidism and on studies focusing mostly in adult patients, in whom the most common coexisting autoimmune diseases were similar to those reported in this study (40).

The strengths of our study include its population-based design, with a large study population including all of the incident cases of hyperthyroidism in children for which treatment was initiated in 2015 in France. As this serious disease is mostly well detected and always

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managed, mostly with drugs in the first line, our indicator provides an exhaustive reflection of the cases of childhood hyperthyroidism treated in France. This study applies a nonlinear model to childhood hyperthyroidism to ensure the retention of as complete a set of information as possible for the explanatory variables. We were also able to study the associated autoimmune conditions at the time of hyperthyroidism diagnosis in the various groups defined based on age and sex.

However, this study also presents several inherent limitations. We cannot exclude the possibility that some of the patients in remission experienced a relapse of hyperthyroidism >24 months after the end of ATD treatment, as reported in adult studies, in which a few relapses have been reported to occur as much as 5 years after the end of ATD treatment (41, 42), although such late relapses are considered unlikely and have never been described in children. It is also possible that some of our patients with hyperthyroidism will go on to develop other autoimmune disorders later in life.

Given the rarity of this disease in very young children, the absolute numbers of very young patients were very low, and this may have affected the estimation of incidence. Moreover, the etiological diagnosis of hyperthyroidism in each individual patient was not validated with patient charts and by differential diagnosis. Exceptional causes of nonautoimmune hyperthyroidism, such as those related to activating mutations of the TSH receptor gene, with severe forms in children diagnosed early in life (43), may have led to incidence being overestimated in very young children.

Another limitation of the indicator used in this study is the potential existence of duplicate cases generated by differences in the identification number (NIR) under which the child is registered. In most cases, the NIR assigned to each child is unique and remains associated with them throughout their lifetime. Otherwise, children may be recorded under several different NIRs, such as those of their parents (both parents for example) to facilitate access to care, leading to possible duplicates and the overestimation of cases. Duplicates undoubtedly accounted for only a very small proportion of the population and are unlikely to have influenced the results. In our study, 8% of the cases were recorded under two different NIRs and 92% under a unique, single NIR. Of the 8% of cases recorded under two different NIRs, 4.5% followed treatment under both NIRs. We therefore assessed the potential overestimation of hyperthyroidism cases at 0.3% (0.08 × 0.04). We therefore believe that our IR estimates are robust.

This study was also limited by the availability of data for only a short period (3 years plus the year underway), restricting data analyses to a single year. We were, therefore, unable to study temporal trends, a prerequisite for any demonstration of an increase in incidence in France.

We now plan to use archived data from SNIIRAM to study cases over a 10-year period. This approach will make it possible to analyze temporal and spatial trends and develop hypotheses concerning possible causes (*e.g.*, the role of EDC exposure).

Conclusion

In conclusion, this population-based study provides epidemiological data for hyperthyroidism in children and adolescents and the estimates of its incidence in France, with robust results. It provides updated results and original data for incidence by age and sex, highlighting the increase in incidence and sex ratio in teenagers. French IRs are slightly higher than expected from the results published for earlier studies in Northern European countries, and further studies are required to determine whether incidence is actually increasing in France. If such an increase is confirmed, it will be interesting to see whether it also concerns the youngest children, as shown, over the last decade for other autoimmune diseases, such as type 1 diabetes (2, 44). The association of hyperthyroidism with other autoimmune conditions and hypotheses concerning links to environmental factors should be investigated over a longer study period.

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